General

Guideline Title

WHO guidelines for treatment of cervical intraepithelial neoplasia 2-3 and adenocarcinoma in situ: cryotherapy, large loop excision of the transformation zone, and cold knife conization.

Bibliographic Source(s)

World Health Organization (WHO). WHO guidelines for treatment of cervical intraepithelial neoplasia 2â€“3 and adenocarcinoma in situ: cryotherapy, large loop excision of the transformation zone, and cold knife conization. Geneva (Switzerland): World Health Organization (WHO); 2014. 34 p. [17 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The definitions for the strength of the recommendations (strong, conditional) and the quality of evidence (high [++++], moderate [+++0], low [++00], and very low [+000]) are provided at the end of the "Major Recommendations" field.

Recommendation 1

The expert panel recommends cryotherapy over no treatment for women who have histologically confirmed cervical intraepithelial neoplasia (CIN) 2 or CIN 3 (collectively referred to as CIN2+) disease (strong recommendation, +000 evidence).

Remarks

This recommendation is strong, although the available evidence was very low quality. The expected benefit of cervical cancer prevention is very high and outweighs harms and any use of resources, but there is uncertainty related to preterm delivery in future pregnancies. However, the panel felt that women would prefer to be treated despite the uncertainty of these risks. This recommendation applies to women regardless of human immunodeficiency virus (HIV) status.

Recommendation 2

The expert panel recommends the loop electrosurgical excision procedure (LEEP) over no treatment for women who have histologically confirmed CIN2+ disease (strong recommendation, ++00 evidence).

Remarks

This recommendation is strong despite low-quality evidence. The benefits outweigh any uncertainty about harms and the use of resources. This recommendation places a high value on women's preference for treatment. This recommendation applies to women regardless of HIV status.

Recommendation 3

The expert panel recommends cold knife conization (CKC) over no treatment for women who have histologically confirmed CIN2+ disease (strong recommendation, +000 evidence)

Remarks

This recommendation considers that no other treatments may be available. In such situations, CKC is recommended over no treatment as the benefits outweigh the harms, and patient preference for treatment was likely to be greater than the preference for no treatment. More data are needed to determine the risk of preterm births, the safety of CKC in settings with differing availability of resources, and whether CKC should be recommended for both CIN 2 and CIN 3. This recommendation applies to women regardless of HIV status.

Recommendation 4

The expert panel suggests cryotherapy or LEEP for women who have histologically confirmed CIN2+ disease (conditional recommendation, +000 evidence).

Remarks

This recommendation is distinct from recommendations made for women who have screened positive without histology or for women with histologically confirmed CIN 1. For women who have histologically confirmed CIN2+, the overall benefits may be greater with LEEP, and adverse events are similar with LEEP or cryotherapy. The availability and implementation of LEEP or cryotherapy will depend on resources. This recommendation applies to women regardless of HIV status.

Recommendation 5

The expert panel recommends cryotherapy over CKC for women who have histologically confirmed CIN2+ disease and for whom cryotherapy or CKC could be appropriate (strong recommendation, +000 evidence).

Remarks

There is low-quality to very-low-quality evidence for the benefits and harms of cryotherapy and CKC. Although there may be fewer recurrences of CIN2+ with CKC than with cryotherapy, the harms may be greater. The resources required are also greater for CKC, including the need for operating rooms, anaesthesia, and highly trained providers or specialists. The limited data on values and preferences of women for either treatment were considered similar. This recommendation applies to women regardless of HIV status.

Recommendation 6

The expert panel recommends LEEP over CKC for women who have histologically confirmed CIN2+ disease and for whom LEEP or CKC could be appropriate (strong recommendation, +000 evidence).

Remarks

The quality of evidence was low for some outcomes and very low for critical outcomes, often with inconsistent results. Therefore, the overall benefits and harms of LEEP over CKC were unclear. Typically, CKC is provided over LEEP for clinical reasons and in specific situations. However, in situations in which there is a choice, the panel agreed that most women would prefer LEEP, as CKC is considered major surgery compared to LEEP. The resources required are also greater with CKC, including anaesthesia, operating rooms, and skilled providers. This recommendation applies to women regardless of HIV status.

Recommendation 7

The expert panel suggests CKC over LEEP for women who have histologically confirmed adenocarcinoma in situ (AIS) disease (conditional recommendation, +000 evidence).

Remarks

This recommendation is based on very low quality evidence, which resulted in imprecise data for the differences in benefits and harms between

CKC and LEEP. CKC may result in fewer recurrences and the panel felt these benefits outweighed the additional resources required for CKC. The preferences of women were also felt to be variable as women in higher income countries may not have as much aversion to CKC (e.g., anaesthesia), while women in lower income countries may prefer LEEP due to the additional risks associated with invasive surgery. This recommendation applies to women regardless of HIV status.

Definitions

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Categories of Quality of Evidence

High (++++): Further research is very unlikely to change confidence in the estimate of effect.

Moderate (+++0): Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low (++00): Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very low (+000): The Guideline Development Group (GDG) is very uncertain about the estimate.

Strength of Recommendations

- Strong: A strong recommendation means that it was clear to the panel that the net desirable consequences of the specified strategy outweighed those of the alternative strategy.
- Conditional: A conditional recommendation was made when it was less clear whether the net desirable consequences of the specified strategy outweighed those of the other strategy.

Interpretation of Strong and Conditional Recommendations

Implications	Strong recommendation "The expert panel recommends… "	Conditional recommendation "The expert panel suggests… "
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences.
For policymakers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Cervical intraepithelial neoplasia (CIN) 2 and CIN 3 (collectively referred to as CIN2+)
- Cervical adenocarcinoma in situ (AIS)

Note: It should be noted that these guidelines focus on treatment of precancerous lesions and of AIS. These guidelines do not address primary prevention of cervical cancer through vaccination against human papillomavirus (HPV).

Guideline Category

Assessment of Therapeutic Effectiveness

Prevention

Treatment

Clinical Specialty

Family Practice

Infectious Diseases

Obstetrics and Gynecology

Oncology

Preventive Medicine

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Nurses

Other

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

To provide recommendations for the use of cryotherapy versus loop electrosurgical excision procedure (LEEP) versus cold knife conization (CKC) for the treatment of histologically confirmed cervical intraepithelial neoplasia (CIN) 2 or CIN 3 (collectively referred to as CIN2+), and additional recommendations for the treatment of histologically confirmed adenocarcinoma in situ (AIS)

Target Population

Women with histologically confirmed cervical intraepithelial neoplasia (CIN) 2 or CIN 3 (collectively referred to as CIN2+) or adenocarcinoma in situ (AIS) regardless of human immunodeficiency virus (HIV) status

Interventions and Practices Considered

1. Cryotherapy
2. Loop electrosurgical excision procedure (LEEP)/large loop excision of the transformation zone (LLETZ)
3. Cold knife conization (CKC)
4. No treatment

Major Outcomes Considered

- Residual/recurrent cervical intraepithelial neoplasia 2-3 (CIN2+) (after 6, 12, and 24 months)
- Damage to other organs/other surgery required, such as injury to bladder or urethra
- Major bleeding (requiring hospitalization/blood transfusion)
- Maternal death
- Human papillomavirus (HPV)-negative status (after 6, 12, and 24 months)
- Major infections (requiring hospital admission and antibiotics)
- Premature delivery
- Fetal/neonatal spontaneous abortions
- Pelvic inflammatory disease (PID)
- Infertility
- Minor bleeding (requires packing or suturing)

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The Methods Group (MG) searched the MEDLINE and EMBASE online databases up to February 2012 for benefits and up to July 2012 for harms of treatment options for cervical intraepithelial neoplasia (CIN) and up to February 2012 for adenocarcinoma in situ (AIS). The search was not restricted by language or study design in order not to exclude primary studies or previously published systematic reviews in this area (see Annex 2 in the original guideline document). Reference lists of relevant studies were reviewed and the Guideline Development Group (GDG) was contacted for additional references.

At least two members of the MG independently screened titles and abstracts and the full text of relevant articles, and a third investigator resolved disagreements. Randomized or quasi-randomized controlled trials, non-randomized studies comparing at least two groups of women receiving different interventions, and non-randomized studies with one group of at least 100 women were included. Studies had to include non-pregnant women aged 18 years or older who had not been previously treated for CIN or AIS. Studies could include women of known or unknown human immunodeficiency virus (HIV) status. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to develop the flow diagram for inclusion and exclusion of studies (see Annex 3 in the original guideline document). A list of all studies included in the reviews is provided in Annex 4 in the original guideline document.

Number of Source Documents

Treatments for Cervical Intraepithelial Neoplasia

A total of 3888 records were identified. An additional 71 records were identified during the update; 611 full-text articles were assessed for

eligibility, and 164 articles were included in the review.

Treatments for Adenocarcinoma in situ

A total of 3888 records were identified. Fifty full-text articles were assessed for eligibility. Thirteen articles were included in the review.

See Annex 3 in the original guideline document for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagrams for inclusion and exclusion of studies for evidence reviews.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Categories of Quality of Evidence

High (++++): Further research is very unlikely to change confidence in the estimate of effect.

Moderate (+++0): Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low (++00): Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very low (+000): The Guideline Development Group (GDG) is very uncertain about the estimate.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Two members of the Methods Group (MG) independently abstracted data about patient characteristics, diagnosis, the surgical interventions, setting, follow-up and outcomes, using a pre-tested data abstraction form. Data to assess the quality of the studies was also collected using the Cochrane risk of bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for non-randomized studies. The MG analysed the data using RevMan 5.1 (review manager software). Relative risks (e.g., risk ratios and odds ratios) were calculated when possible and the effects were normalized over a period of one year. When data were available, subgroup analyses were performed to determine the effects of treatments by human immunodeficiency virus (HIV) status and age. The results of the systematic reviews and of the meta-analysis are being prepared for publication and will be available through the World Health Organization (WHO) Web site .

Two members of the MG evaluated the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and presented the evidence with its quality in GRADE evidence profiles (see Supplemental material [see the "Availability of Companion Documents" field]). The evidence was presented in absolute effects by applying the Risk Ratios to an agreed-upon baseline risk (typically derived from non-randomized studies). Absolute effects over one year and 95% confidence intervals (CI) around that effect were presented as "X/1000 fewer outcomes (95% CI from X to X)". The quality of the evidence or confidence in the effect estimates was assessed as high, moderate, low, or very low, according to the GRADE criteria (see the "Rating Scheme for the Strength of the Evidence" field). Tables to facilitate decision-making for recommendations (evidence-to-recommendations tables) were produced for each recommendation. These tables included a summary of the evidence (benefits and harms), an assessment of the quality of the evidence, relevant patient values and preferences, and any implications for use of resources and feasibility. A summary of the judgements of the Guideline Development Group (GDG) for each recommendation is also provided (see Supplemental material [see the "Availability of Companion Documents" field]).

Methods Used to Formulate the Recommendations

Expert Consensus (Consensus Development Conference)

Description of Methods Used to Formulate the Recommendations

Guideline Groups

The World Health Organization (WHO) formed a Guideline Development Group (GDG). The 17 selected members provided expert clinical guidance and support throughout the guideline development process. WHO also selected an Evidence Review Group (ERG) comprising 33 professionals, including healthcare providers with experience in screening and treating cervical intraepithelial neoplasia (CIN), pathologists, researchers in cervical cancer prevention and treatment, programme directors, health educators, epidemiologists, public health officers, nurses and methodologists. A Methods Group (MG) from the MacGRADE Centre at McMaster University, a WHO collaborating centre, provided expertise in evidence synthesis and guideline development processes.

Formulating Questions and Determining Outcomes

In February 2011, the GDG met to discuss the questions and outcomes to address in the chapter on the treatment of CIN and adenocarcinoma in situ (AIS) to appear in the updated *Comprehensive cervical cancer control: a guide to essential practice* (C4-GEP), in order to incorporate new evidence. The GDG identified nine potential questions to guide the evidence review on the treatment of CIN and AIS. The treatment questions followed the format of PICO (population, intervention, comparison, and outcomes). The population (i.e., women who have histologically confirmed CIN2+ or AIS), intervention (i.e., cryotherapy, loop electrosurgical excision procedure [LEEP], or cold knife conization [CKC]), and comparison group (i.e., other or no treatment) are indicated in Box 1 of the original guideline document, while the priority outcomes are described separately (see Box 2 in the original guideline document and the "Major Outcomes Considered" field).

During this same meeting, the GDG developed a list of outcomes that should be considered when making decisions and recommendations for the treatment strategies. These outcomes were informed by the work previously conducted for the preparation of the 2011 *WHO guidelines: Use of cryotherapy for cervical intraepithelial neoplasia* (see the NGC summary). Following the meeting, the MG surveyed all GDG and ERG members online using Survey Monkey and asked them to identify and rank the critical outcomes for making recommendations. Participants ranked outcomes on a scale from 1 (not at all important) to 7 (critical) in terms of importance for decision-making. Thirty of the 50 members surveyed provided responses and an average ranking was calculated for each outcome. Outcomes with an average ranking of 4 (important) or higher were included for the evidence review and considered when making the recommendations (see Box 2 in the original guideline document and the "Major Outcomes Considered" field).

Synthesis of the Evidence and Preparation of Evidence Profiles

The recommendations were based on questions comparing cryotherapy, LEEP, and CKC to each other and to no treatment for CIN 2 and CIN 3 (collectively referred to as CIN2+) and AIS. The MG therefore searched for, synthesized, analysed, and presented the evidence for benefits and harms, and for patient values and preferences for these different treatment options. However, data for harms were also collected from studies in which treatment was provided for any stage of CIN, as the GDG indicated during a guideline development meeting in April 2012 that harms of treatments are unlikely to depend on the stage of CIN. Issues relating to resource use and feasibility were identified and summarized by the WHO Steering Group, the GDG, and the ERG.

Development of the Recommendations

In early 2012 (26–28 April), the GDG, the ERG and the MG met to discuss the recommendations. One member each from the GDG and the MG chaired the meeting, which was attended by experts from around the world, representing various public health and medical disciplines. Members of the MG presented evidence profiles and evidence-to-recommendation tables, which included the evidence about the benefits and harms, values and preferences, resources and feasibility.

After the April 2012 meeting, more work was done to finalize the remarks and to confirm the data on harms. An update of the search was performed and the recommendations did not change after considering the additional evidence.

WHO has recently developed the WHO cervical cancer prevention and control costing tool. This tool includes two modules: one on the cost of human papillomavirus (HPV) vaccination and the other on the cost of a screen-and-treat programme. The purpose of the tool is to help programme managers develop a budget for the programme. In order to develop the tool, the cost of each intervention was collected, including detailed costing of surgery, for a range of countries and the calculation tables developed. This, in addition to the experience of the members of the ERG, was essential to the discussion of the resources needed for each of the treatments.

Recommendations were made by the GDG and ERG by balancing the overall desirable and undesirable consequences of each treatment, which included consideration of important outcomes, values and preferences, resources and feasibility, along with the level of certainty of that information.

Members of the panel discussed the consequences and reached consensus for the final recommendations. In rare cases of disagreement, members voted and discussed until there was 100% agreement. The results of those discussions are documented in the evidence-to-recommendation tables for each recommendation, available online in the Supplemental material (see the "Availability of Companion Documents" field). The GDG and ERG also identified key research gaps.

The recommendations were assessed as 'strong' or 'conditional' in accordance with the *WHO handbook for guidelines development* (see the "Availability of Companion Documents" field). Strong recommendations have been worded as 'the expert panel recommends' and conditional recommendations as 'the expert panel suggests'. A strong recommendation means that it was clear to the panel that the net desirable consequences of the specified strategy outweighed those of the alternative strategy. But a conditional recommendation was made when it was less clear whether the net desirable consequences of the specified strategy outweighed those of the other strategy. In this guideline, many recommendations are conditional (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

- Strong: A strong recommendation means that it was clear to the panel that the net desirable consequences of the specified strategy outweighed those of the alternative strategy.
- Conditional: A conditional recommendation was made when it was less clear whether the net desirable consequences of the specified strategy outweighed those of the other strategy.

Interpretation of Strong and Conditional Recommendations

Implications	Strong recommendation "The expert panel recommends… "	Conditional recommendation "The expert panel suggests… "
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences.
For policymakers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

Cost Analysis

The World Health Organization (WHO) has recently developed the WHO cervical cancer prevention and control costing tool. This tool includes two modules: one on the cost of human papillomavirus (HPV) vaccination and the other on the cost of a screen-and-treat programme. The purpose of the tool is to help programme managers develop a budget for the programme. In order to develop the tool, the cost of each intervention was collected, including detailed costing of surgery, for a range of countries and the calculation tables developed. This, in addition to the experience of the members of the Evidence Review Group (ERG), was essential to the discussion of the resources needed for each of the treatments. Refer to the "Resource implications" sections of the Supplemental Material (see the "Availability of Companion Documents" field) for judgements on each recommendation made by the expert panel.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Guideline Review and Approval Process

This guideline underwent the following peer review process before and during development:

The questions formulated for the development of the guidelines were circulated among the World Health Organization (WHO) Steering Group, who also discussed them with the Guideline Development Group (GDG). When the GDG and the WHO Steering Group had reached agreement on the questions, these were sent to the External Review Group (ERG).

The protocol for systematic reviews was circulated among the GDG. This protocol was also discussed during the ERG meeting, which was also attended by the European Guidelines Development Group in addition to the WHO Steering Group, the GDG and the Methods Group (MG). During that meeting the evidence that had been identified and the draft evidence profiles were discussed.

Discussions and conference calls were regularly held with the GDG to discuss the data from the literature review, the Grading of Recommendations Assessment, Development and Evaluations (GRADE) evidence profiles, and the recommendations.

The final draft guideline with the recommendations was circulated among the members of the GDG for review before WHO clearance. No disagreements were noted.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of cryotherapy, loop electrosurgical excision procedure (LEEP), large loop excision of the transformation zone (LLETZ), and cold knife conization (CKC) in the treatment of cervical intraepithelial neoplasia 2-3 (CIN2+) and adenocarcinoma in situ (AIS)

See the "Remarks" and "Summary of the evidence" sections of the original guideline document as well as the supplemental material for details on the balance of benefits versus harms of specific interventions (see the "Availability of Companion Documents" field).

Potential Harms

- Major and minor adverse events may occur rarely with cryotherapy. It was unclear whether there is a difference in spontaneous abortion and infertility, but there may be 55/1000 more preterm deliveries (from 38 fewer to 1000 more) with cryotherapy.
- Premature delivery may be increased with the loop electrosurgical excision procedure (LEEP) compared to no treatment based on 8 non-randomized studies with a risk ratio of 1.85 (95% confidence interval [CI]: 1.59–52.15), which means there may be 37/1000 more preterm deliveries (from 26 to 51 more). The effect of LEEP on spontaneous abortion and infertility is unclear, as is the effect on human papillomavirus (HPV) clearance at 6 or 12 months. There may be little to no difference in major infections, major bleeding, or damage to organs requiring surgery. However, minor bleeding may be increased (200 more women with minor bleeding per 1000).
- Cold knife conization (CKC) treatment may be associated with: major bleeding (9/1000 more, 25 studies), major infections (9/1000 more,

9 studies), minor bleeding (24/1000 more, 8 studies), and damage to organs (3/1000 more, 27 studies). According to three non-randomized studies, CKC may carry a higher risk of premature delivery (risk ratio 3.41; 95% CI: 2.38–34.88) and a higher risk of spontaneous abortion compared to no treatment.

- Although there may be fewer recurrences of cervical intraepithelial neoplasia 2-3 (CIN2+) with CKC than with cryotherapy, the harms may be greater. Indirect evidence from a systematic review of premature delivery showed that there may be less risk of premature delivery (<37 weeks) with cryotherapy: 45/1000 fewer preterm deliveries over 12 months. Up to 44 studies contributed data on harms and showed that there may be fewer women who have major bleeding requiring hospital admission or blood transfusion with cryotherapy (8/1000 fewer) as well as fewer major infections (7/1000 fewer), fewer women with damage to other organs requiring surgery (3/1000 fewer), and fewer women who have minor bleeding (23/1000 fewer).

See the "Remarks" and "Summary of the evidence" sections of the original guideline document as well as the supplemental material for details on the balance of benefits versus harms of specific interventions (see the "Availability of Companion Documents" field).

Qualifying Statements

Qualifying Statements

- The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization (WHO) concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
- The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.
- All reasonable precautions have been taken by the WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the WHO be liable for damages arising from its use.
- The Guideline Development Group (GDG) identified and prioritized treatment outcomes that were important to the decision-making process. For many of these outcomes, in particular fertility and reproductive outcomes, there was low-quality to very-low-quality data, or no data. There was also little research about the effects of the treatments in women of human immunodeficiency virus (HIV)-positive status, and few studies had measured the potential for HIV transmission following treatment. Much of the data came from non-randomized studies based on single groups of women receiving treatment without an independent comparison group. This meant that many comparisons between surgical treatments – cryotherapy versus loop electrosurgical excision procedure (LEEP), for example – were made by comparing the results from single-arm non-randomized studies of cryotherapy to single-arm non-randomized studies of LEEP. When comparing these studies, it is often unclear whether the populations, settings, interventions, and outcomes are adequately similar. The results were therefore assessed as inconsistent and/or indirect, leading to low- to very-low-quality evidence.

Implementation of the Guideline

Description of Implementation Strategy

Guideline Dissemination

These guidelines will be available online at the World Health Organization (WHO) Library database and there will be a link on WHO's Sexual and Reproductive Health Web page and in the WHO Reproductive Health Library (RHL), an electronic review journal. The publication will also be announced in the United Nations Development Programme (UNDP)/United Nations Population Fund (UNFPA)/United Nations Children's Fund (UNICEF)/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) WHO Reproductive Health Update, which reaches more than 2000 subscribers and numerous organizations with whom WHO is working. Many of these organizations will also copy the announcement in their newsletters.

The guidelines will be distributed in print to subscribers to WHO publications, to the WHO mailing list for mandatory free distribution (national chief health executives, ministers of health or directors-general of health, depository libraries for WHO publications, WHO representatives/liaison

officers, WHO headquarters library, WHO regional offices, and off-site office libraries), additional non-mandatory free recipients (competent national authorities for sexual and reproductive health, cancer control programmes, national research centres in reproductive health, and WHO collaborating centres), WHO staff at headquarters regional and country offices and elsewhere, concerned non-governmental organizations (NGOs), medical societies concerned with cancer control and/or sexual and reproductive health, scientific journals (including general medical journals and journals specialized on sexual and reproductive health or cancer), international organizations, and donors, potential donors, potential publishers of translated versions, as well as all those who contributed to the documents.

Conference invitations to discuss and present the guidelines will be accepted.

Regional conferences have already been held in the Americas and Africa in 2013, to present the new recommendations to a number of stakeholders involved in national programme planning. The other regions will be covered in 2014.

If requested by regional offices, countries will be supported to adapt the guideline to their country-specific needs and to integrate the material with existing national guidelines. Adaptation will be done by organizing regional, sub-regional and country-level workshops for discussion of each recommendation, in order to adapt them to the national epidemiologic, cultural, and socioeconomic context.

Initially, the guidelines will be available in English only and translations will be developed subject to the availability of funding. Translation into non-United Nations (UN) languages and publication in these languages by third parties will be encouraged.

Implementation Tools

Foreign Language Translations

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

World Health Organization (WHO). WHO guidelines for treatment of cervical intraepithelial neoplasia 2â€“3 and adenocarcinoma in situ: cryotherapy, large loop excision of the transformation zone, and cold knife conization. Geneva (Switzerland): World Health Organization (WHO); 2014. 34 p. [17 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014

Guideline Developer(s)

World Health Organization - International Agency

Source(s) of Funding

The Flanders International Cooperation Agency (FICA), the Institut National du Cancer (INCa), France, and the Global Alliance for Vaccines and Immunisation (GAVI) provided the main funding for this document.

Guideline Committee

Guideline Development Group

World Health Organization (WHO) Steering Group

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Financial Disclosures/Conflicts of Interest

Management of Conflicts of Interest

Conflicts of interest were managed as follows:

1. All experts who participated in the process were required to complete the World Health Organization (WHO) Declaration of Interest (DOI) form before they commenced their work for WHO, and to promptly notify WHO if any change in the disclosed information occurred during the course of this work. The completed DOI forms were reviewed by the WHO Secretariat with a view to managing disclosed interests in the field of cervical cancer screening and treatment.
2. At the meeting of the External Review Group (ERG) in September 2010 and at the first joint meeting of the Guideline Development Group (GDG), Methods Group (MG) and the ERG in 2013, each expert disclosed his/her declared interests to the other experts as part of the round of introductions at the beginning of the meeting so that the group was aware of any existing interests among the members.
3. All declared interests have been reviewed by WHO's Office of the Legal Counsel. The decision was that all experts could participate in the process but interests should be disclosed in the guideline.
4. All relevant declared interests (15 out of 54 experts) are disclosed and summarized in this report (see Annex 1 of the original guideline document).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the World Health Organization (WHO) Web site .

Print copies: Available from the WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; Phone: +41 22 791 3264; Fax: +41 22 791 4857; E-mail: bookorders@who.int.

Availability of Companion Documents

The following are available:

- WHO handbook for guideline development. Geneva (Switzerland): World Health Organization (WHO); 2012. 56 p. Electronic copies: Available from the World Health Organization (WHO) Web site .
- WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ. Supplemental material: GRADE evidence-to-recommendation tables and evidence profiles for each recommendation. Geneva (Switzerland): World Health Organization (WHO); 2014. 38 p. Electronic copies: Available from the WHO Web site .
- WHO cervical cancer prevention and control costing (C4P) tool user's guide. Geneva (Switzerland): World Health Organization; May 2012. 34 p. Electronic copies: Available in English and French from the WHO Web site.

Patient Resources

None available

NGC Status

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